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Comparative activity of the penem antibiotic Sch 34343 against Gram-negative and Gram-positive bacteria with special reference to multiresistant strains

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A new penem antibiotic, Sch 34343, was shown to be active against a large number of Gram-positive bacteria. The drug inhibited penicillinase-positive and -negative staphylococci equally well, being five times more active than cefamandole and ten times more active than methicillin. Most methicillin-resistant staphylococci were inhibited by concentrations between 0·25 and 4 mg/l, but a small group of highly resistant strains were observed. Sch 34343 was eight times less active than ampicillin and penicillin G, but as active as piperacillin against enterococci. The drug showed excellent activity against various streptococci. Sch 34343 was as bactericidal as flucloxacillin, ampicillin and penicillin G against staphylococci, enterococci and streptococci, respectively, in killing kinetic tests Enterobacteriaceae susceptible to third-generation cephalosporins were approximately five times less susceptible to Sch 34343, but MICs were far below the susceptibility breakpoint. Sch 34343 was equally active against *Citrobacter* and *Enterobacter* strains that were highly resistant to third-generation cephalosporins and to aztreonam. Together with thienamycin, this drug seems to be a good alternative for the treatment of infections caused by bacteria resistant to third-generation cephalosporins and to aztreonam.

Introduction

Sch 34343 is a new penem antibiotic which is chemically related to the carbapenem antibiotic thienamycin. This study was undertaken to compare the *in-vitro* efficacy of Sch 34343 with various other β-lactam antibiotics. Some 250 clinical isolates of Gram-positive organisms were included in the study to provide a good indication of the potential efficacy of the drug in the therapy of Gram-positive infections. Special emphasis was given to the bactericidal activity of the drug against Gram-positive bacteria. The activity of Sch 34343 was also examined against Enterobacteriaceae including a small collection of multiply-resistant organisms, which were resistant to the third-generation cephalosporins, aztreonam and often also to aminoglycosides.

Methods

Bacteria

The bacteria used were isolated from clinical material and identified according to standard procedures. Two hundred and sixty eight Gram-positive organisms were examined. The collection of Gram-negative bacilli comprised *Escherichia coli* (24),

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Klebsiella pneumoniae (21), *K. oxytoca* (10), *K. ozaenae* (4), *Enterobacter cloacae* (29), *Ent. aerogenes* (13), *Ent. agglomerans* (11), *Citrobacter freundii* (50), *Citro. diversus* (6), *Citrobacter* spp. (5), *Serratia marcescens* (16), *Ser. liquefaciens* (6), *Proteus mirabilis* (17), *Pr. vulgaris* (22), *Morganella morganii* (4), *Providentia rettgeri* (7), and *Prov. stuartii* (6). Strains susceptible to third-generation cephalosporins were fresh clinical isolates. Strains resistant to cephalosporins were derived from worldwide sources.

Antibiotics

Stock solutions of Sch 34343, imipenem, penicillin G, ampicillin, piperacillin, oxacillin, flucloxacillin, methicillin, cephalothin, cefamandole, cefotaxime, ceftriaxone, cefoperazone, ceftazidime, latamoxef (moxalactam), and aztreonam were prepared in sterile distilled water and either used immediately or stored at −80°C, if necessary. All drugs were provided by the pharmaceutical companies.

Minimal inhibitory concentration tests

Minimal inhibitory concentrations (MICs) were determined by serial two-fold dilutions of antibiotics, usually in Mueller–Hinton agar (BBL) or broth. Pneumococci and haemolytic streptococci were tested on agar containing 1% (w/v) IsoVitaleX (BBL) and 1% (w/v) haemoglobin (BBL). The inoculum in agar dilution was about 10^4 per spot, and in macro-broth dilution 5×10^5 to 10^6 per ml. MICs were read after incubation at 35°C for 18–24 h. The MIC techniques corresponded to the procedures proposed by the National Committee of Clinical Laboratory Standards (1983).

Bactericidal tests

The concentrations that killed 99% and 99·9% of the inoculum were determined by plating 100 and 10 µl of the broth from each tube of the macro dilution test showing no growth on blood agar. Before plating, 200 µl of an enzyme solution containing approximately 8 (if concentrations of drugs were < 10 mg/l) or 80 (if concentrations were > 10 mg/l) units of penicillin amido-β-lactamhydrolase E.C. 3.5.2.6. from *Bacillus cereus* 569/H9 (Genzyme Biochemicals Ltd., Springfield Mill, Maidstone) per ml were added to the broth tubes and incubated at room temperature for 5 min. This served to destroy any drug and, thus, to avoid carry-over of bacteriostatic activity.

Kinetics of killing was investigated in 20 ml of Mueller–Hinton broth, unsupplemented or supplemented with IsoVitaleX and haemoglobin (see above) when necessary. Four times the MIC of the various drugs were added. At appropriate time intervals, samples were withdrawn, incubated with the *B. cereus* enzyme as described and plated undiluted or in appropriate dilutions.

Population analysis

Populations of methicillin-resistant staphylococci were analysed by disaggregation of overnight broth cultures (briefly, by ultra sonication at 20 kHz) and surface inoculation of appropriate dilutions on drug-containing Mueller–Hinton agar plates. Colony counts after 48 h of incubation at 30 or 37°C allowed calculation of the number of viable units among 10^8 cfu resistant to each concentration of antimicrobial agent.

Table I. Comparative activity of Sch 34343 and other β-lactam antibiotics against Gram-positive bacteria

Organism (no. of isolates)	Drug	MIC (mg/l)[a] Mean	Mode	Range	MIC_{50}[b]	MIC_{90}[b]
Staph. aureus						
penicillinase-negative (13)	Sch 34343	0·11	0·12	0·06–0·25	0·12	0·12
	imipenem	0·08	0·12	0·03–0·12	0 06	0·12
	penicillin G	0·02	0 03	0·01–0·06	0 01	0·01
	methicillin	1	1	0 5–2	0·5	1
	cefamandole	0·21	0·25	0·12–0·25	0 12	0·25
Staph. aureus						
penicillinase-positive (20)	Sch 34343	0·15	0·12	0·06–0·5	0·12	0·25
	imipenem	0·09	0·12	0·03–0·12	0·06	0·12
	methicillin	1·68	2	1–2	1	2
	cefamandole	0·5	0 5	0·25–2	1	2
	cefotaxime	2 2	2	2–4	2	2
Staph aureus						
methicillin-resistant (39)	Sch 34343	0·69	*	0 12–256	0·5	4
	Sch 34343 (30°C)	1 6	*	0·5–256	1	4
	imipenem	0·23	*	0·06–128	0 12	1
	methicillin	4·76	*	1–256	4	8
	cefamandole	1 9	*	0·25–256	1	4
	cefotaxime	21·2	*	8–256	32	64
Staph epidermidis						
penicillinase-negative (14)	Sch 34343	0·23	0·12	0·06–1	0 25	0·5
	imipenem	0·07	0·03	0·03–1	0 06	0 25
	penicillin G	0·02	0·03	0·01–0 12	0 01	0·06
	methicillin	1·77	1	0·5–8	1	4
	cefamandole	0·27	0·25	0·06–1	0 12	0 5
Staph. epidermidis						
penicillinase-positive (27)	Sch 34343	0·13	0·12	0·06–0·25	0 12	0 25
	imipenem	0·12	0·01	0·01–0·25	0·06	0·25
	methicillin	2·19	2	0·5–16	1	4
	cefamandole	0·27	0·25	0·06–2	0 12	0 5
	ceftriaxone	2·1	2	0·25–16	2	8
Staph. epidermidis						
methicillin-resistant (14)	Sch 34343	5·4	*	1–128	4	8
	imipenem	2	*	0 06–32	2	16
	ceftriaxone	17 6	*	4–256	8	128
Str faecalis (31)	Sch 34343	5·9	4	4–32	4	8
	imipenem	2·4	2	1–4	2	4
	penicillin G	1·9	2	1–2	1	2
	ampicillin	0·9	1	0·5–2	0 5	1
	piperacillin	5·9	4	1–8	4	8
	cefamandole	25	32	16–32	16	32

Table I. (*continued*)

Organism (no. of isolates)	Drug	MIC (mg/l)[a] Mean	Mode	Range	MIC_{50}[b]	MIC_{90}[b]
Str. faecium (14)	Sch 34343	32	*	4–256	32	128
	imipenem	6·9	*	0·03–64	8	32
	penicillin G	3·4	*	0·25–16	2	16
	ampicillin	0·4	*	0·5–16	2	8
	piperacillin	13·8	*	1–64	16	32
	cefamandole	74	*	2–256	64	256
Str. pyogenes (18)	Sch 34343	0·06	0·06	0·03–0·12	0·06	0·06
	imipenem	0·05	0·03	0·03–0·12	0·03	0·12
	penicillin g	0·01	0·01	0·01	0·01	0·01
	cefamandole	0·05	0·06	0·01–0·12	0·03	0·12
	ceftriaxone	0·03	0·03	0·03	0·03	0·03
Str. agalactiae (9)	Sch 34343	0·15	0·12	0·12–0·25	0·12	0·25
	imipenem	0·42	0·5	0·25–0·5	0·5	0·5
	penicillin G	0 03	0·03	0·03	0 03	0 03
	cefamandole	0 13	0·12	0·03–0·12	0·06	0·25
	ceftriaxone	0 25	0·25	0·25	0·25	0·25
Str. pneumoniae (28)	Sch 34343	0·07	0·06	0·03–0·5	0·06	0·25
	imipenem	0·11	0·06	0·03–0·5	0·06	0·25
	penicillin G	0·01	0·01	0·01–0·03	0·01	0·01
	cefamandole	0·03	0·06	0·01–0·25	0·03	0·12
	ceftriaxone	0·03	0·03	0·01–0·25	0·03	0·03
Corynebacterium JK (12)	Sch 34343	369	256	128–256	256	256
	imipenem	362	256	128–256	256	256
Corynebacterium unspecified (34)	Sch 34343	6·7	*	0·03–256	1	256
	imipenem	2·4	*	0·03–256	0·25	256

[a] Data obtained with the agar dilution procedure of the National Committee of Clinical Laboratory Standards (1983). Incubation was carried out at 35°C, unless otherwise indicated, for 18–24 h

[b] Concentration required to inhibit 50 or 90% of the examined strains, respectively

* Wide range of MICs

Results

Comparison of Sch 34343 with other β-lactam antibiotics against Gram-positive bacteria

Table I summarizes MICs of Sch 34343 and other drugs against Gram-positive bacteria. As can be seen, the drug showed excellent activity against staphylococci, whether they produced penicillinase or not. The drug was 15 times more active than methicillin and exhibited two to four times better activity than cefamandole against methicillin-susceptible cultures. Imipenem was either two to four times more active or showed equal activity to Sch 34343. Imipenem and Sch 34343 also showed some activity against methicillin-resistant *Staph. aureus* and *Staph. epidermidis*, when tested in agar dilution with an inoculum of 10^4 per spot and incubated for 24 h at 35°C. Incubation of plates for 48 h or incubation at 30°C increased MICs by a factor of

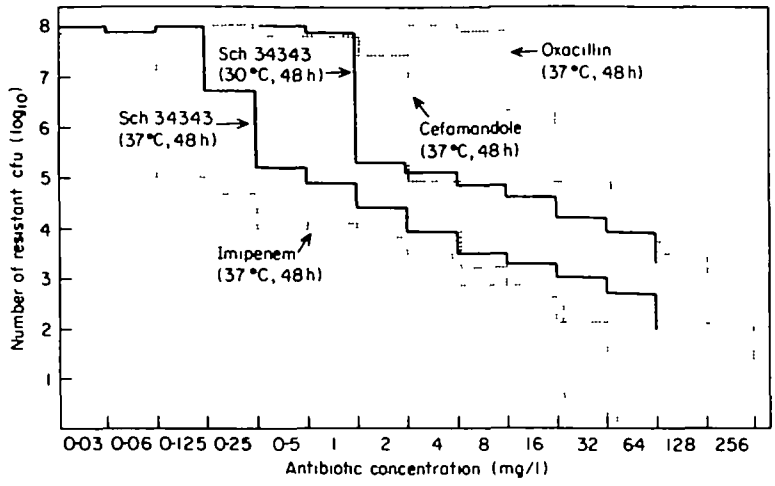

Figure 1. Composition of highly methicillin-resistant *Staph aureus* strain EK 695 of cells with different levels of resistance to Sch 34343, imipenem, cefamandole and oxacillin

5–10. These two drugs were slightly more active than cefamandole, which was shown elsewhere to be one of the most active β-lactam drugs against methicillin-resistant staphylococci (Kayser, 1980).

Heterogeneity amongst the methicillin-resistant staphylococci was observed with Sch 34343. The drug was more active than cefamandole and oxacillin and of similar activity to imipenem in these population studies (Figure 1).

Although Sch 34343 was not as potent as penicillin or ampicillin against the enterococci, it showed some activity, equal to that of piperacillin, and ten times or more the activity of the cephalosporins. Imipenem also proved to have moderate activity against enterococci.

Sch 34343 and imipenem were equally active against various species of streptococci. However, penicillin G still remained the most potent agent against these organisms.

Although corynebacteria are generally contaminants in microbiological samples, group JK cornynebacterium has been associated with severe infections, particularly in immunosuppressed patients (Young *et al.*, 1981). The organism has also been isolated occasionally from cases of peritonitis in patients undergoing continuous ambulatory peritoneal dialysis (Pierard *et al.*, 1983). These organisms have been found to be resistant to many antimicrobials including the aminoglycosides and β-lactam antibiotics. JK cornynebacteria were also found to be highly resistant to Sch 34343 and to imipenem. Other unspecified corynebacteria, which were isolated from infectious lesions and, thus, might have played a role in disease, exhibited strain-dependent susceptibility or resistance to both drugs.

Bactericidal activity of Sch 34343

Examination of the bactericidal activity of Sch 34343 and comparative agents was carried out in conventional MBC tests (Anhalt, Sabath & Barry, 1980) in triplicate Although great care was taken in performing these tests, results were often inconsistent, due to multiple methodological problems (Taylor *et al.*, 1983; Kayser &

Table II. Bactericidal activity of Sch 34343 in comparison with penicillin G, ampicillin and flucloxacillin against Gram-positive bacteria

Organism	MIC (mg/l)[a]		MBC_{99} (mg/l)[b]		$MBC_{99.9}$ (mg/l)[b]	
	Sch 34343	Comparative drug[c]	Sch 34343	Comparative drug[c]	Sch 34343	Comparative drug[c]
Staph. aureus 41 penicillinase-positive	0·12	0·25	2	0·25	> 64	> 64
Staph. aureus 61 penicillinase-negative	0·06	0·25	0 25	0 25	> 64	0·25
Staph. epidermidis 145 penicillinase-positive	0·06	0·25	1	1	32	4
Staph. epidermidis 162 penicillinase-negative	0·12	0·5	1	1	1	16
Str. faecalis 97	8	1	64	32	> 64	> 64
Str. faecium 128	16	2	> 64	> 64	> 64	> 64
Str. pyogenes 193	0·12	0·03	1	0·03	> 64	0·25
Str agalactiae 219	0·12	0·06	1	0·25	1	0·5
Str. pneumoniae 241	0·01	0·03	0·03	0·01	0 03	0 01
Str. mutans 349	0·06	0·03	0·25	> 64	> 64	> 64

[a] Minimal inhibitory concentration determined in macro-broth dilution according to the NCCLS procedure.
[b] Concentration necessary to kill 99 or 99 9% of the inoculum, respectively.
[c] Comparative drug for staphylococci was flucloxacillin, for enterococci ampicillin and for streptococci penicillin G.

Müller, 1983). Table II summarizes some of the results obtained. With the exception of enterococci, Sch 34343 showed good bactericidal activity at the 99% killing level. At the 99·9% level, however, it was often not bactericidal even at high concentrations. Sometimes the comparative agent also was not bactericidal at this level. Sometimes Sch 34343 was active, but the comparative drug was not. No paradoxical effect (Eagle & Musselman, 1948) was observed with strains and drugs examined. We therefore decided to study the bactericidal potential of Sch 34343 in a kinetic system. Figure 2 shows that Sch 34343 extensively killed the organisms examined with a rate identical to that of the comparative drugs.

Comparison of Sch 34343 with other β-lactam antibiotics against Gram-negative bacteria

Recent reports have shown that Enterobacteriaceae can become resistant to third-generation cephalosporins by mutation in a chromosomal locus, regulating the production of a cephalosporinase (Seeberg, Tolxdorff-Neutzling & Wiedemann, 1983). The frequency of resistant mutants of this type in clinical isolates is still low (Kayser & Kohler, 1984). They have mainly been observed in *Citrobacter* and *Enterobacter* species. We collected such strains from our area and from worldwide sources and examined the activity of Sch 34343 against them. Table III summarizes the results obtained. For comparative purposes, data about the activity of the advanced β-lactam antibiotics against strains of Enterobacteriaceae susceptible to third-generation

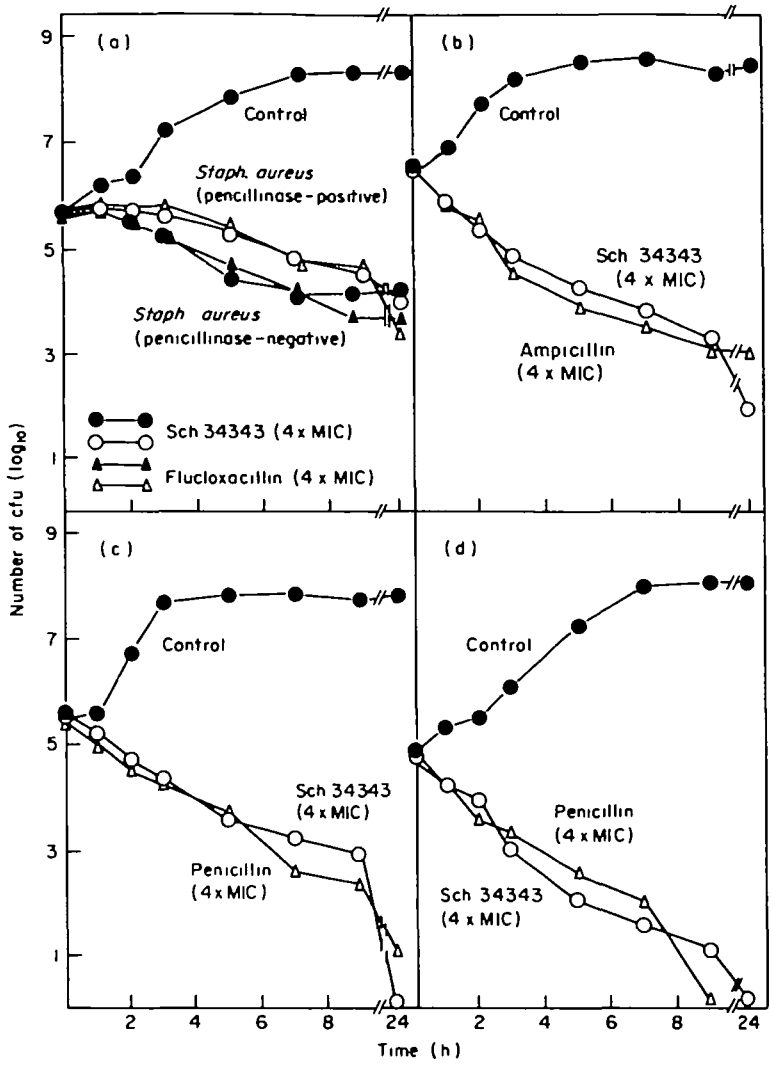

Figure 2. Rates of killing of *Staph. aureus, Str. faecalis, Str. pyogenes* and *Str. pneumoniae* by Sch 34343 (○——○) and flucloxacillin (△——△), ampicillin (△——△) and penicillin G (△——△), respectively (*a*) Open symbols: *Staph aureus* 41 (penicillinase-positive) MIC of Sch 34343 = 0 125 and of flucloxacillin = 0·25 mg/l Closed symbols *Staph. aureus* 61 (penicillinase negative). MIC of Sch 34343 = 0 06 and flucloxacillin = 0 25 mg/l (*b*) *Str faecalis* 97 MIC of Sch 34343 = 8 and of ampicillin = 1 mg/l. (*c*) *Str. pyogenes* 193 MIC of Sch 34343 = 0·125 and of penicillin G = 0·03 mg/l (*d*) *Str pneumoniae* 241. MIC of Sch 34343 = 0·008 and of penicillin G = 0·03 mg/l

cephalosporins have been included. It can be seen that Sch 34343 was not as active as third-generation cephalosporins and aztrenonam on a weight basis against susceptible organisms. MICs of Sch 34343, however, were in a range easily obtained in tissue by normal dosing (Investigational Brochure, Schering Corp., Kenilworth, NJ). However, Sch 34343 and imipenem were only slightly less active against organisms highly resistant to third-generation cephalosporins and to aztreonam, than against the susceptible group.

Table III. Comparison of Sch 34343 with other β-lactam antibiotics against Gram-negative bacteria susceptible or resistant to third-generation cephalosporins

Organism[a] (no. of isolates)	Drug	MICs (mg/l) of susceptible isolates			MICs (mg/l) of resistant isolates		
		Mean	Mode	Range	Mean	Mode	Range
E. coli	Sch 34343	0·6	1	0·12–16			
no. sensitive (24)	imipenem	0·2	0·12	0·06–1			
	cefotaxime	0·1	0·12	0·03–2			
	cefoperazone	1·7	*	0·12–64			
	ceftriaxone	0·1	0·12	0·03–0·25			
	ceftazidime	0·3	0·12	0·03–2			
	latamoxef	0·2	0·25	0·06–0·25			
	aztreonam	0·2	0·12	0·03–1			
Klebsiella spp.	Sch 34343	0·3	0·25	0·12–1	1		
no. sensitive (34)	imipenem	0·2	0·25	0·12–1	0·5		
no. resistant (1)	cefotaxime	0·1	0·06	0·01–2	16		
	cefoperazone	4·7	*	0·12–256	16		
	ceftriaxone	0·3	0·06	0·03–64	16		
	ceftazidime	0·4	0·25	0·06–2	16		
	latamoxef	0·3	0·06	0·03–2	16		
	aztreonam	0·6	0·06	0·03–64	4		
Enterobacter spp.	Sch 34343	0·7	0·5	0·12–4	2·1	1	0·5–16
no. sensitive (27)	imipenem	0·4	0·25	0·06–4	0·4	0·5	0·12–2
no. resistant (26)	cefotaxime	0·2	*	0·01–8	85·6	128	16–> 256
	cefoperazone	0·3	0·25	0·01–16	36·5	32	2–> 256
	ceftriaxone	0·2	0·12	0·01–16	73·0	128	8–> 256
	ceftazidime	0·6	0·25	0·06–64	50·2	64	4–> 256
	latamoxef	0·3	0·12	0·06–32	9·9	8	1–128
	aztreonam	0·2	0·12	0·03–16	26·5	*	1–256
Serratia spp.	Sch 34343	1·8	2	0·5–16	16		
no. sensitive (21)	imipenem	0·4	0·25	0·25–4	1		
no resistant (1)	cefotaxime	0·4	0·25	0·06–8	16		
	cefoperazone	8·8	16	0·5–64	16		
	ceftriaxone	0·3	0·12	0·03–8	4		
	ceftazidime	0·3	0·06	0·06–16	16		
	latamoxef	0·6	0·25	0·06–256	256		
	aztreonam	0·3	0·12	0·06–4	2		
Citrobacter spp.	Sch 34343	0·5	0·5	0·12–2	0·8	1	0·25–4
no. sensitive (43)	imipenem	0·3	0·25	0·12–1	0·3	0·25	0·12–1
no. resistant (18)	cefotaxime	0·2	0·12	0·01–8	38·5	32	16–128
	cefoperazone	1·1	0·25	0·06–32	47·2	32	16–> 256
	ceftriaxone	0·1	0·06	0·01–16	40·2	32	16–256
	ceftazidime	0·45	0·25	0·06–16	38·8	*	0·06–> 256
	latamoxef	0·2	0·12	0·06–8	3·7	*	0·12–64
	aztreonam	0·2	0·06	0·03–32	13·2	*	0·25–> 256

Table III. (*continued*)

Organism[a] (no. of isolates)	Drug	MICs (mg/l) of susceptible isolates			MICs (mg/l) of resistant isolates		
		Mean	Mode	Range	Mean	Mode	Range
Pr. mirabilis	Sch 34343	0·9	0·5	0·25–2			
no. sensitive (17)	imipenem	0·7	0·5	0·06–4			
	cefotaxime	0·02	0·01	0·01–0·06			
	cefoperazone	0·4	0·25	0·12–8			
	ceftriaxone	0·01	0·01	0·01			
	ceftazidime	0·04	0·03	0·01–0·5			
	latamoxef	0·1	0·12	0·06–0·25			
	aztreonam	0·02	0·01	0·01–0·03			
Pr. vulgaris	Sch 34343	0·8	0·5	0·5–4			
Morg. morganii	imipenem	0·6	1	0·03–4			
Providencia spp.	cefotaxime	0·02	0·01	0·01–0·25			
no. sensitive (39)	cefoperazone	0·6	0·5	0·06–8			
	ceftriaxone	0·02	0·01	0·01–0·25			
	ceftazidime	0·05	0·03	0·01–2			
	latamoxef	0·4	0·25	0·03–0·5			
	aztreonam	0·04	0·01	0·01–4			

[a] Number of isolates susceptible (MIC $\leq$ 8 mg/l) or resistant (MIC $>$ 8 mg/l) to cefotaxime.
[b] Wide range of MICs.

Discussion

Sch 34343 has been shown in this study to be an excellent antibiotic against most species of Gram-positive bacteria. In particular, it exhibited some activity against methicillin-resistant staphylococci, although the typical characteristics of these bacteria—heterogeneity and influence of incubation temperature on phenotypic expression of resistance—were also observed with Sch 34343. The drug was only three to four times less active than imipenem against methicillin-resistant staphylococci in agar dilution tests, but the numbers of sub-populations resistant to each drug were the same (see Figure 1). These two drugs, therefore, could be considered as a possible choice in the treatment of infections caused by such bacteria in exceptional cases, if for instance other antimicrobials such as vancomycin, could not be used. The general rule, however, that infections by methicillin-resistant staphylococci should not be treated with any β-lactam agent, is valid for Sch 34343 and imipenem. Sch 34343 exhibited high activity against streptococci and pneumococci, but enterococci were not as susceptible as towards penicillin G or ampicillin. Against *Streptococcus faecalis*, however, the drug was as active as piperacillin.

Sch 34343 was as bactericidal as comparative agents (flucloxacillin, ampicillin and penicillin (G) against representative Gram-positive bacteria in the kinetic studies. The variable results obtained with Sch 34343 and the comparative drugs in conventional MBC 99·9% tests reflect the laboratory problems connected with this procedure (Taylor *et al.*, 1983; Kayser & Müller, 1983).

Although Sch 34343 was approximately five times less active than third-generation cephalosporins against Enterobacteriaceae, MICs were far below the susceptibility

threshold. MICs were not (or only by one dilution) elevated against *Citrobacter* and *Enterobacter* strains, highly resistant to third-generation cephalosporins. This behaviour reflects the extreme stability of the drug to β-lactamases, since it has been shown that cephalosporin resistance in such strains is due to chromosomal cephalosporinase (Sanders & Sanders 1983, Seeberg *et al.*, 1983). Sch 34343, thus, together with imipenem, can be considered as potent chemotherapeutic agents in infections caused by Enterobacteriaceae resistant to third-generation cephalosporins and to aztreonam.

References

Anhalt, J. P., Sabath, S. D & Barry, A. L. (1980). Special tests: bactericidal activity, activity of antimicrobics in combination and detection of β-lactamase production In *Manual of Clinical Microbiology* (E. H. Lennette, A. Balows, W. J. Hausler Jr. & J. P. Truant, Eds), pp. 478–84. American Society of Microbiology, Washington D.C.

Eagle, H. & Musselman. A. D. (1948). The rate of bactericidal action of penicillin *in vitro* as a function of its concentration, and its paradoxically reduced activity at high concentrations against certain organisms. *Journal of Experimental Medicine* **88**, 99–131.

Kayser, F. H. (1980). Die Resistenz Methicillin-resistenter Staphylokokken gegenüber neuen Cephalosporin-Antibiotika *Infection* **8**, 165–70.

Kayser, F. H. & Müller, F. (1983). Resistance and tolerance of the staphylococcus to β-lactam antibiotics. In *Proc. 13th International Congress of Chemotherapy,* Vienna, 1983 (K. H. Spitzy & K. Karrer, Eds), Symposium no. 45), Staphylococcal Infections, pp. 8–14.

Kayser, F. H. & Kohler, M. (1984). Vergleich der antibakteriellen Aktivitäten der Cephalosporine. *Schweizerische Medizinische Wochenschrift* **114**, 156–61.

National Committee of Clinical Laboratory Standards (NCCLS) (1983). Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. Tentative Standard M7-T. *The National Committee of Clinical Laboratory Standards,* Vol. 3, No. 2.

Pierard, D., Lauwers, S., Mouton, M., Sennesael, J. & Verbeelen, D. (1983). Group JK corynebacterium peritonitis in a patient undergoing continuous ambulatory peritoneal dialysis. *Journal of Clinical Microbiology* **18**, 1011–4.

Sanders, C. C. & Sanders, W. E (1983). Emergence of resistance during therapy with the newer β-lactam antibiotics: role of inducible β-lactamases and implications for the future. *Review of Infectious Diseases* **5**, 639–48.

Seeberg, A. H., Tolxdorff-Neutzling, R. M. & Wiedemann, B. (1983). Chromosomal β-lactamase of *Enterobacter cloacae* are responsible for resistance to third-generation cephalosporins. *Antimicrobial Agents and Chemotherapy* **23**, 918–25

Taylor, P. C., Schoenknecht, F. D., Sherris, J. C. & Linner, E. C. (1983). Determination of minimum bactericidal concentration of oxacillin for *Staphylococcus aureus*: influence and significance of technical factors. *Antimicrobial Agents and Chemotherapy* **23**, 142–50.

Young, V. M., Meyers, W. F., Moody, M.R. & Schimpff S. C. (1981). The emergence of coryneform bacteria as a cause of nosocomial infection in compromised hosts. *American Journal of Medicine* **70**, 646–50.